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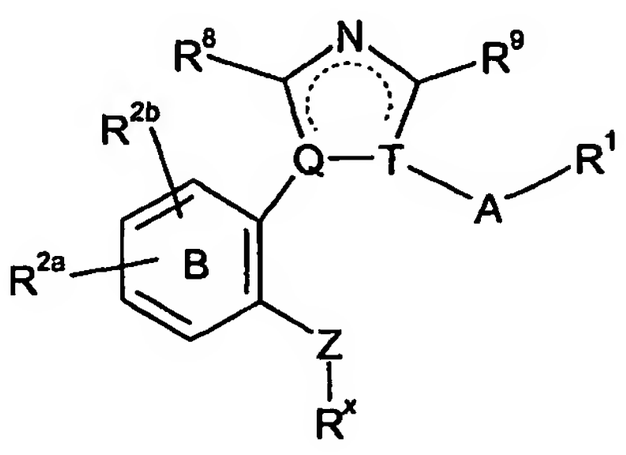
(54) Title: IMIDAZOLE COMPOUNDS



(I)

(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable derivative thereof: wherein A, B, Z, R1, R2a, R2b, Rx, R8, R9, Q, and T are as defined in the specification, a process for the preparation of such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine.

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IMIDAZOLE COMPOUNDS

This invention relates to imidazole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of conditions mediated by the action of PGE_2 at EP_1 receptors.

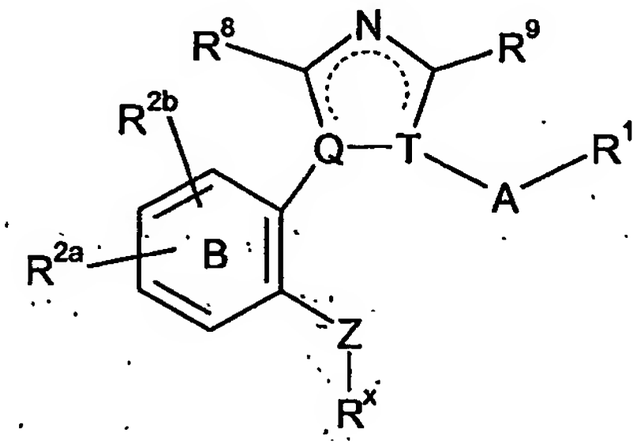
The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4). The EP_1 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP_1 receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* Ṡ Narumiya et al, Physiological Reviews 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology,*1994, 112, 735- 740 suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation*, 2001, 107 (3), 325 shows that in the EP_1 knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP_1 receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar *et al* in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP_1 receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDS and/or COX-2 inhibitors.

In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE_2-induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor. WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

It is now suggested that a novel group of imidazole derivatives surprisingly are selective for the EP_1 receptor over the EP_3 receptor, and are therefore indicated to be useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors. Such conditions include pain, or inflammatory, immunological, bone, neurodegenerative or renal disorders.

Accordingly the present invention provides compounds of formula (I):



(I)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO_2;

R^1 represents CO_2R^4, CN, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

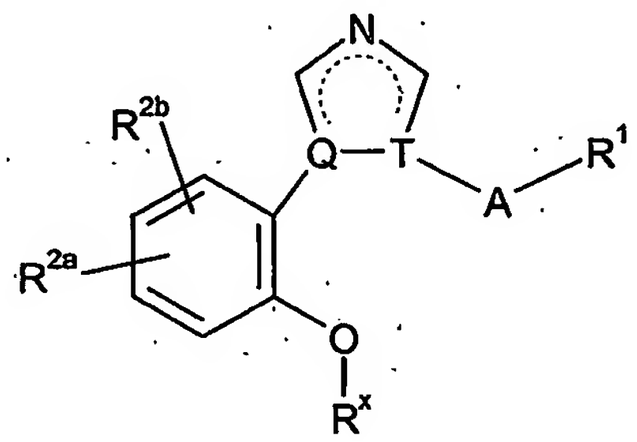
R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted

SO_2heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR^7;
R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
either Q is carbon and T is nitrogen, or
Q is nitrogen and T is carbon; and
the dotted line represents alternating single and double bonds;
R^8 and R^9 independently represent hydrogen, halogen, C_{1-3}alkyl or CF_3;
Q^a and Q^b are independently selected from hydrogen and CH_3;
wherein when A is a 6-membered ring the R^1 substituent and imidazole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and imidazole ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
and derivatives thereof.

In one aspect the present invention provides compounds of formula (Ia):



(Ia)

wherein:
A represents an optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;
R^1 represents CO_2R^4, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, $CONR^5R^6$, 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;
R^{2a} and R^{2b} independently represents halo, optionally substituted alkyl, CN, SO_2R^5, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;
R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR^4, O or SO_n, wherein n is 0, 1 or 2: or R^x may be optionally substituted CQ_2-heterocyclyl or optionally substituted CQ_2-phenyl wherein Q is independently selected from hydrogen and CH_3;
R^4 represents hydrogen or an optionally substituted alkyl;
R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or an optionally substituted alkyl, optionally substituted SO_2aryl, optionally substituted SO_2heterocyclyl group, CN, optionally substituted CH_2aryl or COR^7;
R^7 represents hydrogen, optionally substituted heteroaryl or optionally substituted aryl;
either Q is carbon and T is nitrogen, or
Q is nitrogen and T is carbon; and
the dotted line represents alternating single and double bonds;
wherein when A is a 6-membered ring the R^1 and imidazole group are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 and imidazole group are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
and derivatives thereof.

When A is a six membered ring, preferably R^1 is attached to the group A in the 3 position relative to the bond attaching A to the imidazole ring.

Suitably A is selected from phenyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl, all of which may be optionally substituted. More suitably A is pyridyl or an optionally substituted phenyl; most suitably A is optionally substituted phenyl.

Optional substituents for A include up to four substituents, preferably 0 or 1 substituent, independently selected from halogen, CN, optionally substituted CO_2C_{1-6}alkyl, $CONR^5R^6$, NR^5R^6, optionally substituted NR^5COC_{1-6}alkyl, optionally substituted NR^5COphenyl, optionally substituted NR^5COpiperidinyl, optionally substituted NR^5COheterocyclyl, optionally substituted $NR^5SO_2C_{1-6}$alkyl, OH, optionally substituted OC_{1-6}alkyl, optionally substituted C_{1-6}alkyl and $NR^{10}R^{11}$ wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, wherein R^5 and R^6 are as defined above for compounds of formula (I).

In an alternative aspect, optional substituents for A when a phenyl group include up to four substituents, preferably 0 or 1 substituent, independently selected from halogen, NR^5R^6, NR^5COC_{1-6}alkyl, $NR^5SO_2C_{1-6}$alkyl, OR^5, C_{1-6}alkyl and $NR^{10}R^{11}$ wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, wherein R^5 and R^6 are as defined above.

In one aspect, optional substituents for A when a 5- or 6-membered heterocyclyl group include NH_2. When A is pyridyl it may be substituted on the ring nitrogen by an oxygen to give a pyridine N-oxide.

When R^x represents an optionally substituted alkyl this group is preferably C_{1-8}alkyl, suitably the alkyl group is CH_2C_{5-6}cycloalkyl.

Suitably R^x includes optionally substituted C_{1-6}alkyl, optionally substituted CH_2phenyl, CH_2pyridyl, or CH_2thienyl.

More suitably R^x represents CH_2phenyl optionally substituted by one, two or three, preferably one or two substituents selected from Cl, Br, F, CF_3, C_{1-4}alkyl and OC_{1-4}alkyl, or R^x is CH_2C_{5-6}cycloalkyl.

Suitably A is phenyl.

Suitably B is phenyl.

Suitably Z is O.

Suitably R^1 represents CO_2R^4, wherein R^4 is hydrogen or C_{1-4}alkyl. More suitably R^1 represents CO_2H.

Suitably R^{2a} is hydrogen.

Suitably R^{2b} is selected from hydrogen, CF_3 and halogen, e.g. chloro and bromo. More suitably R^{2b} is selected from hydrogen and halogen, e.g. chloro and bromo

Suitably R^{2b} is positioned 1,4-relative to the Z substituent and 1,3-relative to the imidazole ring.

Suitably R^{3a} and R^{3b} are each hydrogen.

Suitably R^4 represents hydrogen or C_{1-3}alkyl, more preferably R^4 is hydrogen.

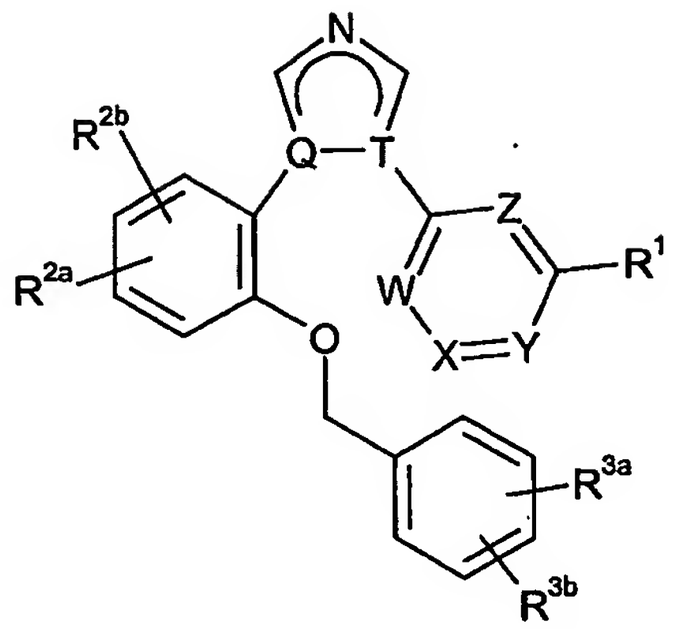
Suitably R^5 represents hydrogen or C_{1-3}alkyl.

Suitably R^6 represents hydrogen or C_{1-3}alkyl.

Suitably R^7 represents hydrogen.

Suitably R^8 and R^9 are each selected from hydrogen, Cl, CH_3 or CF_3. More suitably R^8 and R^9 each represents hydrogen.

In another aspect, compounds of formula (I) are compounds of formula (Ib):



(Ib)

wherein:

R^1 is CO_2R^4;

R^{2a} and R^{2a} are independently selected from hydrogen, halo, optionally substituted C_{1-6}alkyl, CN or $SO_2(C_{1-6})$alkyl;

R^{3a} and R^{3b} independently represents halo or an optionally substituted $O(C_{1-6})$alkyl, or C_{1-6}alkyl;

R^4 is hydrogen or an optionally substituted C_{1-6}alkyl;

W, X, Y and Z represents CH or N wherein at least one of W, X, Y or Z is CH;

either Q is carbon and T is nitrogen, or

Q is nitrogen and T is carbon; and

the dotted line represents alternating single and double bonds;

and derivatives thereof.

In one aspect the derivatives are pharmaceutically acceptable derivatives.

Suitably R^{3a} and R^{3b} independently represent hydrogen, halo or optionally substituted $O(C_{1-6})$alkyl.

Preferably R^4 is hydrogen.

Compounds of formula (I) include:

3-[5-(2-Benzyloxy-phenyl)-imidazol-1-yl]-benzoic acid;

3-[5-(2-Benzyloxy-5-chloro-phenyl)-imidazol-1-yl]-benzoic acid;

3-[5-(2-Benzyloxy-5-bromo-phenyl)-imidazol-1-yl]-benzoic acid;

3-[5-(2-Benzyloxy-phenyl)-3*H*-imidazol-4-yl]-benzoic acid; and

derivatives thereof.

Preferably compounds are selective for EP_1 over EP_3. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP_1 over EP_3.

Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I).

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be pharmaceutically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic,

stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

The terms "halogen" or "halo" are used to represent fluorine, chlorine, bromine or iodine, more preferably fluorine, chlorine or bromine.

The term "alkyl" as a group or part of a group means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof such as cyclohexylmethyl and cyclopentylmethyl. Unless otherwise defined, preferably "alkyl" is C_{1-8}alkyl, more preferably "alkyl" is C_{1-6}alkyl.

The term "alkoxy" as a group or part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group. Preferably "alkoxy" is C_{1-6} alkoxy.

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents. Examples of 5- membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

The term "aryl" as a group or part of a group means a 5- or 6- membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be optionally substituted by

one or more substituents, for example up to 4, 3 or 2 substituents. Preferably the aryl group is phenyl.

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents, for example up to 3 or up to 2 substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, indolyl, and indazolyl.

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

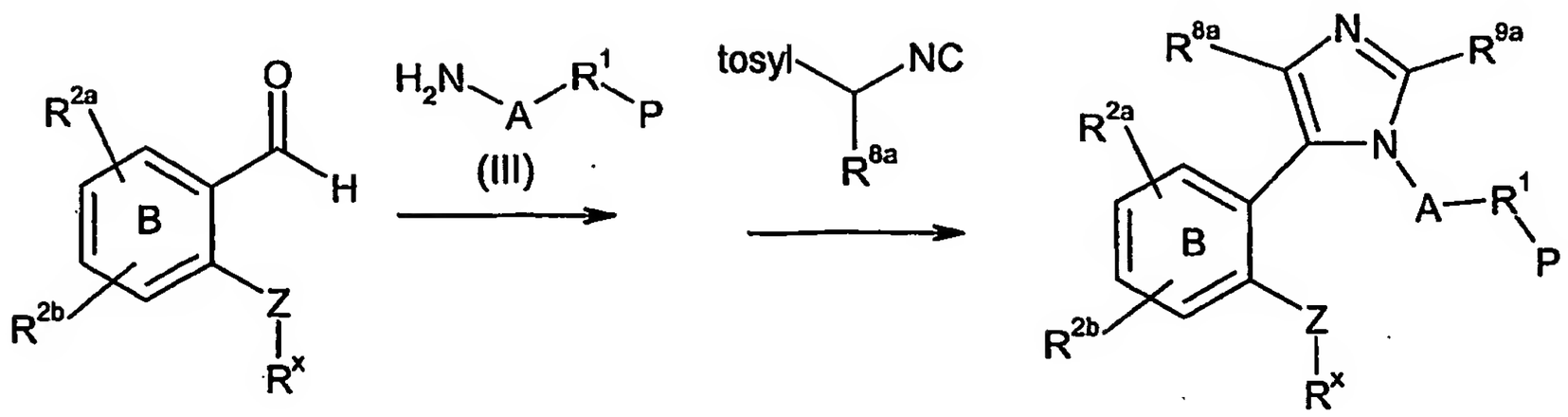
When the heteroatom nitrogen replaces a carbon atom in an alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group, the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C_{1-8}alkyl, preferably hydrogen and C_{1-6}alkyl, more preferably hydrogen.

Optional substituents for alkyl groups unless hereinbefore defined are OH, CO_2R^4, NR^4R^5, (O), OC_{1-6}alkyl or halo, wherein R^4 and R^5 are as herein before defined. An alkyl or alkenyl group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents.

Unless otherwise defined, optional substituents for aryl, heteroaryl or heterocyclyl moieties as a group or part of a group are selected from optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkoxy and halogen. Alternative optional substituents include C_{1-6}alkyl, C_{1-6}alkoxy and halogen.

Compounds of formula (I) can be prepared as set forth in the following schemes and in the examples. The following processes form another aspect of the present invention.

Compounds of formula (I) wherein Q is carbon and T is nitrogen [also referred to as compounds of formula (IA)] may be prepared as set forth in the following scheme:



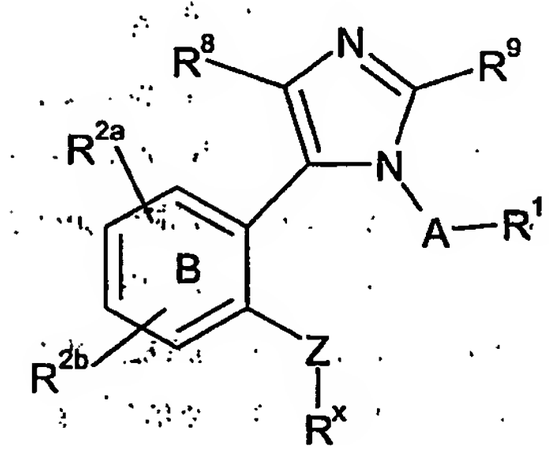
(IV) (IIA)

R^{8a} = hydrogen or C_{1-3}alkyl

R^{9a} = hydrogen

Optional introduction of alternative R^8 and /or R^9 groups

Deprotection



(IA)

wherein P is an optional protecting group; and A, B, Z, R^{2a}, R^{2b}, R^1, R^8, R^9 and R^x are as defined for compounds of formula (I).

Compounds of formula (IA) wherein R^8 is Cl may be prepared, for example, by treating a compound of formula (IIA) wherein R^{8a} is hydrogen with a source of electrophilic chlorine, e.g. N-chlorosuccinimide, followed if necessary by deprotection.

Compounds of formula (IA) wherein R^8 is F may be prepared, for example, by treating a compound of formula (IIA) wherein R^{8a} is hydrogen with a source of electrophilic fluorine, e.g. SELECTFLUOR ™ [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)], followed if necessary by deprotection.

Compounds of formula (IA) wherein R^8 is CF_3 may be prepared, for example, by treating a compound of formula (IIA) wherein R^{8a} is hydrogen with N-iodosuccinimide followed by

isopropyl magnesium chloride, followed by sequential treatment with CO_2 then SF_4 and subsequent deprotection if necessary.

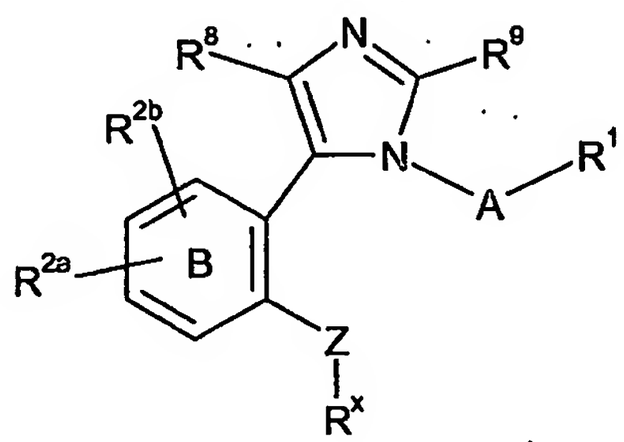
Compounds of formula (IA) wherein R^9 is Cl may be prepared, for example, by treating a compound of formula (IIA) with lithium diisopropylamide followed by a source of electrophilic chlorine, e.g. N-chlorosuccinimide, followed if necessary by deprotection.

Compounds of formula (IA) wherein R^9 is F may be prepared by treating a compound of formula (IIA) with lithium diisopropylamide followed by a source of electrophilic fluorine, e.g. SELECTFLUOR ™ [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)], followed if necessary by deprotection.

Compounds of formula (IA) wherein R^9 is C_{1-3}alkyl may be prepared, for example by treating a compound of formula (IIA) with lithium diisopropylamide followed by a C_{1-3}alkyl iodide, followed if necessary by deprotection.

Compounds of formula (IA) wherein R^9 is CF_3 may be prepared, for example by treating a compound of formula (IIA) with lithium diisopropylamide followed by sequential treatment with CO_2 then SF_4, followed if necessary by deprotection.

Accordingly the present invention also provides a process for the preparation of a compound of formula (IA) or a derivative thereof:



(IA)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

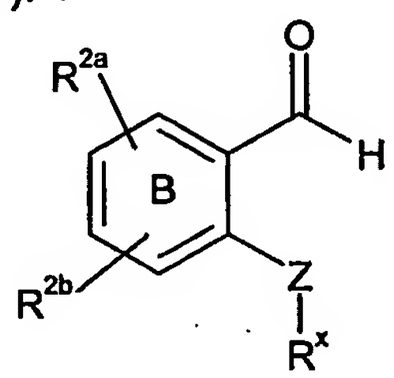
B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO_2;

R^1 represents CO_2R^4, CN, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

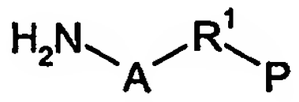
R^{2a} and R^{2b} independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;
R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;
R^4 represents hydrogen or an optionally substituted alkyl;
R^5 represents hydrogen or an optionally substituted alkyl;
R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR^7;
R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
R^8 and R^9 independently represent hydrogen, halogen, C_{1-3}alkyl or CF_3;
Q^a and Q^b are independently selected from hydrogen and CH_3;
wherein when A is a 6-membered ring the R^1 substituent and imidazole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and imidazole ring are attached to substitutable carbon atoms 1,2- or 1;3- relative to each other:

comprising
reacting a compound of formula (IV):



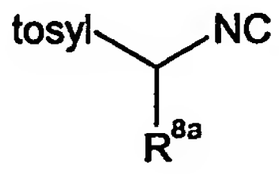
(IV)

wherein B, R^{2a}, R^{2b}, Z, and R^x are as defined for compounds of formula (IA),
with a compound of formula (III):



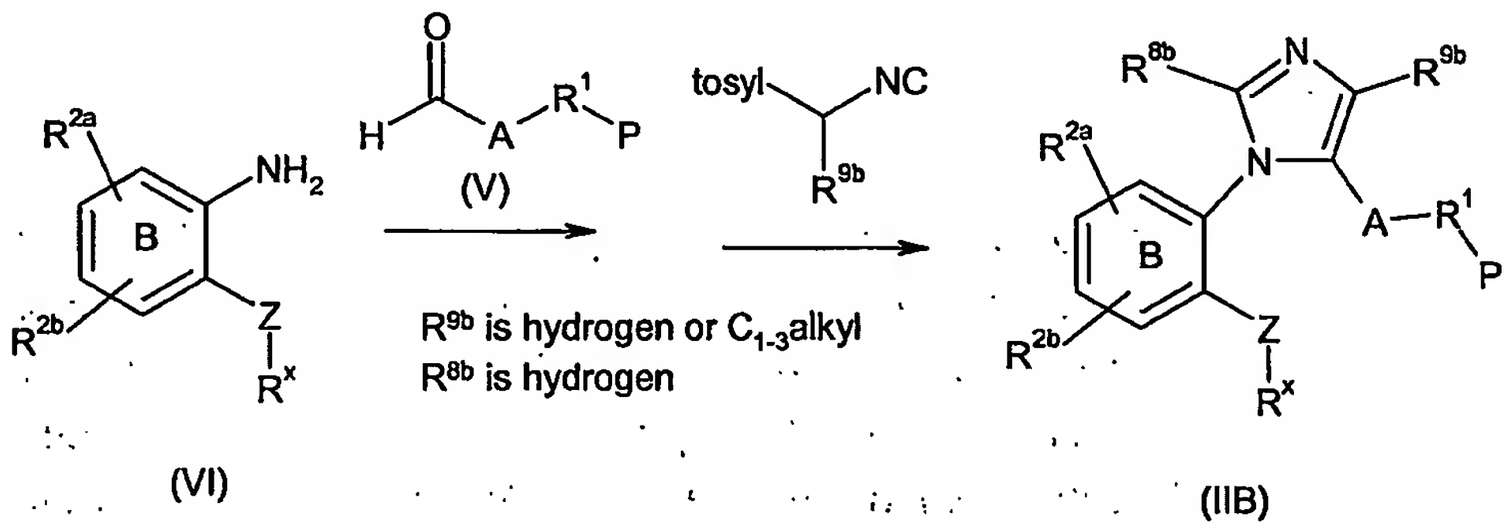
(III)

wherein A and R^1 are as hereinbefore defined for a compound of formula (IA) and P is an optional protecting group;
and a tosylmethylisocyanide:



wherein R^{8a} is hydrogen or C_{1-3}alkyl;
and where required, and in any order, converting:
a group R^{8a} to a group R^8;
a group R^{9a} to a group R^9, and/or
one group R^x to another group R^x;
and where required carrying out the following optional steps in any order:
effecting deprotection; and/or
converting one group R^1 to another group R^1; and/or
forming a derivative of the compound of formula (IA) so formed.

Compounds of formula (I) wherein Q is nitrogen and T is carbon [also referred to as compounds of formula (IB)] may be prepared as set forth in the following scheme.



wherein P is a protecting group; and A, B, Z, R^{2a}, R^{2b}, R^1, R^9, R^8 and R^x are as defined for compounds of formula (I).

Compounds of formula (IB) wherein R^9 is Cl may be prepared, for example, by treating a compound of formula (IIB) wherein R^{9b} is hydrogen with a source of electrophilic chlorine, e.g. N-chlorosuccinimide, followed if necessary by deprotection.

Compounds of formula (IB) wherein R^9 is F may be prepared, for example, by treating a compound of formula (IIB) wherein R^{9b} is hydrogen with a source of electrophilic fluorine, e.g. SELECTFLUOR ™ [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)], followed if necessary by deprotection.

Compounds of formula (IB) wherein R^9 is CF_3 may be prepared, for example, by treating a compound of formula (IIB) wherein R^{9b} is hydrogen with N-iodosuccinimide followed by isopropyl magnesium chloride, followed by sequential treatment with CO_2 then SF_4 , followed by deprotection if necessary.

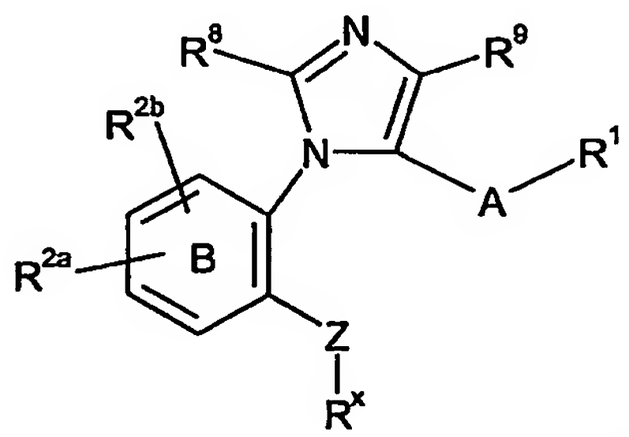
Compounds of formula (IB) wherein R^8 is Cl may be prepared, for example, by treating a compound of formula (IIB) with lithium diisopropylamide followed by a source of electrophilic chlorine, e.g. N-chlorosuccinimide, followed if necessary by deprotection.

Compounds of formula (IB) wherein R^8 is F may be prepared by treating a compound of formula (IIB) with lithium diisopropylamide followed by a source of electrophilic fluorine, e.g. SELECTFLUOR ™ [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)], followed if necessary by deprotection.

Compounds of formula (IB) wherein R^8 is C_{1-3}alkyl may be prepared, for example by treating a compound of formula (IIB) with lithium diisopropylamide followed by a C_{1-3}alkyl iodide, followed if necessary by deprotection.

Compounds of formula (IB) wherein R^8 is CF_3 may be prepared, for example by treating a compound of formula (IIB) with lithium diisopropylamide followed by sequential treament with CO_2 then SF_4, followed if necessary by deprotection.

Accordingly the present invention also provides a process for the preparation of a compound of formula (IB) or a derivative thereof:

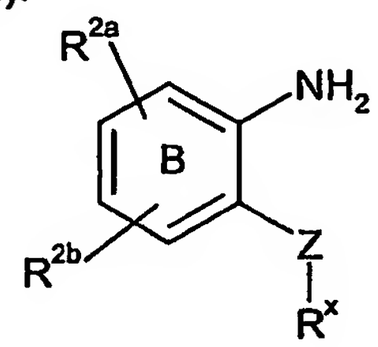


(IB)

wherein:

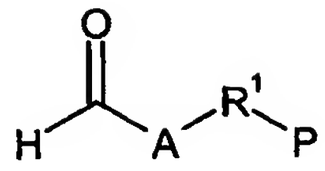
A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;
B represents a phenyl or pyridyl ring;
Z represents O, S, SO, or SO_2;
R^1 represents CO_2R^4, CN, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;
R^{2a} and R^{2b} independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;
R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;
R^4 represents hydrogen or an optionally substituted alkyl;
R^5 represents hydrogen or an optionally substituted alkyl;
R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR^7;
R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
R^8 and R^9 independently represent hydrogen, halogen, C_{1-3}alkyl or CF_3;
Q^a and Q^b are independently selected from hydrogen and CH_3;
wherein when A is a 6-membered ring the R^1 substituent and imidazole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and imidazole ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other:

comprising:
reacting a compound of formula (VI):



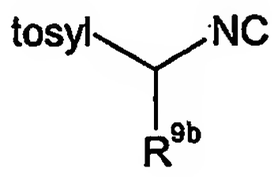
(IV)

wherein B, R^{2a}, R^{2b}, Z, and R^x are as defined for compounds of formula (IB),
with a compound of formula (V):



(V)

wherein A and R^1 are as hereinbefore defined for a compound of formula (IB) and P is an optional protecting group;
and a compound:



wherein R^{9b} is hydrogen or C_{1-3}alkyl;
and where required, and in any order, converting:
a group R^{8b} to a group R^8;
a group R^{9b} to a group R^9, and/or
one group R^x to another group R^x;
and where required carrying out the following optional steps in any order:
effecting deprotection; and/or
converting one group R^1 to another group R^1; and/or
forming a derivative of the compound of formula (IB) so formed.

It will be appreciated that certain substituents in intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art.

A group R^1 may be converted to another group R^1 by use of conventional organic transformations known to those skilled in the art and as described in, for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of substituents which may be converted include one group R^x to another group R^x; and one substituent on a group A to another substituent on a group A. Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

For example, when R^x is p-methoxybenzyl, cleavage of the ether to give the phenol or pyridinol is carried out using, for example, using acid e.g. HCl/dioxane or HBr/acetic acid. When R^x is methyl, cleavage of the ether to give the phenol is carried out using, for

example, sodium methanethiolate. Cleavage of the ether to give a pyridinol is carried out in the presence of, for example, trifluoroacetic acid. Conversion to another R^x group, for example a substituted benzyl group, may be effected by reaction of the phenol or pyridinol with a suitable substituted benzyl bromide. The skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When R^x is benzyl, cleavage of the ether to give the phenol or pyridinol may be carried out by hydrogenation according to known methods e.g. H_2-Pd/C or NH_4CO_2H-Pd/C. The resulting phenol or pyridinol can then be converted to another group R^x as described above.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

When R^1 is CO_2H examples of P include methyl, ethyl or substituted benzyl esters.

Suitable reaction conditions for the deprotection of a compounds of formula (IIa) and (IIb) include heating in ethanolic sodium hydroxide solution.

Imidazole functionalisation is described in, for example, *J. Med. Chem.*, 2003, 46, 3463-3475, and in patent applications WO 00/23426 and WO 01/70704.

Suitable conditions for the reaction of a compound of formula (IV) with a compound of formula (III) to give a compound of formula (IIa), or a compound of formula (VI) with a compound of formula (V) to give a compound of formula (IIb), include heating with sodium sulfate in a solvent, for example toluene, followed by treatment by heating with a tosylmethyl isocyanide in a solvent such as ethanol in the presence of a base, for example potassium carbonate (D. Van Leusen and A.M. Van Leusen, *Organic Reactions*, vol 57, 417-666, L. Overman (Ed.).

Compounds of formula (III), (IV), (V), and (VI) are commercially available, or readily prepared by conversion of commercially available starting materials by methods known to those skilled in the art.

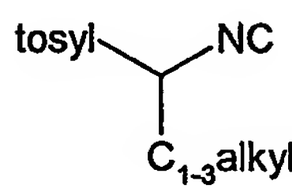
For example, amines of formula (III) and formula (VI) may be made by methods described in *The Amino Group*, S. Patai (Ed), Interscience, New York 1968, and references cited therein. The preparation of amines is also described in Richard Larock, *Comprehensive*

Organic Transformations, 2nd edition, pages 753 to 879, Wiley-VCH, ISBN 0-471-19031-4.

Aldehydes of formula (IV) or formula (V) may be made by methods described in *The Chemistry of the Carbonyl Group*, S. Patai (Ed), Interscience, New York, 1966, and references cited therein.

Tosylmethyl isocyanide (TosMIC) is commercially available.

Compounds of the formula:



may be prepared by alkylation of TosMIC with a C_{1-3}alkyl iodide, for example under phase transfer catalysis conditions (*Tetrahedron*, 1988, 44(23), 7243-7254).

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention bind to the EP_1 receptor and they are therefore considered to be useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors.

Conditions mediated by the action of PGE_2 at EP_1 receptors include pain; fever; inflammation; immunological diseases; abnormal platelet function diseases; impotence or erectile dysfunction; bone disease; hemodynamic side effects of non-steroidal anti-inflammatory drugs; cardiovascular diseases; neurodegenerative diseases and neurodegeneration; neurodegeneration following trauma; tinnitus; dependence on a dependence-inducing agent; complications of Type I diabetes; and kidney dysfunction.

The compounds of formula (I) are considered to be useful as analgesics. They are therefore considered useful in the treatment or prevention of pain.

The compounds of formula (I) are considered useful as analgesics to treat acute pain, chronic pain, neuropatic pain, inflammatory pain, visceral pain, pain associated with cancer and fibromyalgia, pain associated with migraine, tension headache and cluster headaches,

and pain associated with functional bowel disorders, non-cardiac chest pain and non-ulcer dispepsia.

The compounds of formula (I) are considered useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention are considered to be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) are also considered useful in the treatment of fever.

The compounds of formula (I) are also considered useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme,

ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also considered useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also considered useful in the treatment of diseases relating to abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also considered useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also considered useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also considered useful in the treatment of bone disease characterised by abnormal bone metabolism or resorbtion such as osteoporosis (especially postmenopausal osteoporosis); hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) are also considered useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also considered useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also considered useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor

neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also considered useful in the treatment of neuroprotection and in the treatment of neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also considered useful in the treatment of tinnitus.

The compounds of formula (I) are also considered useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also considered useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also considered useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP_1 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B ssubtype; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

EXAMPLES

Abbreviations:
Bn (benzyl), Bu, Pr, Me, Et (butyl, propyl, methyl ethyl), DMSO (dimethyl sulfoxide), DCM (dichloromethane), DME (ethylene glycol dimethyl ether), DMF (N,N-dimethylformamide), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), EtOAc (ethyl acetate), EtOH (ethanol), HPLC (High pressure liquid chromatography), LCMS (Liquid chromatography/Mass spectroscopy), MDAP (Mass Directed Purification), MeOH (methanol), NMR (Nuclear Magnetic Resonance (spectrum)), Ph (phenyl), pTSA (para-toluene sulphonic acid), SPE (Solid Phase Extraction), TBAF (tetrabutylammonium fluoride), THF (tetrahydrofuran), s, d, t, q, m, br (singlet, doublet, triplet, quartet, multiplet, broad.)

Mass Directed Auto-purification systems

Hardware
Waters 600 gradient pump
Waters 2700 sample manager
Waters Reagent Manager
Micromass ZMD mass spectrometer
Gilson 202 - fraction collector
Gilson Aspec - waste collector

Software
Micromass Masslynx version 3.5

Column
The column used is typically a Supelco ABZ+ column whose dimensions are 10mm internal diameter by 100mm in length. The stationary phase particle size is 5µm.

Solvents
A. Aqueous solvent = Water + 0.1% Formic Acid
B. Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid
Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate
Needle rinse solvent = MeOH: Water: DMSO (N,N-dimethyl sulfoxide) 80:10:10

Methods
There are five methods used depending on the analytical retention time of the compound of interest.
They all have a 15-minute runtime, which comprises of a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

MDP 1.5-2.2 = 0-30%B

MDP 2.0-2.8 = 5-30% B
MDP 2.5-3.0 = 15-55%B
MDP 2.8-4.0 = 30-80% B
MDP 3.8-5.5 = 50-90% B

Flow rate

All of the above methods have a flow rate of 20ml/min.

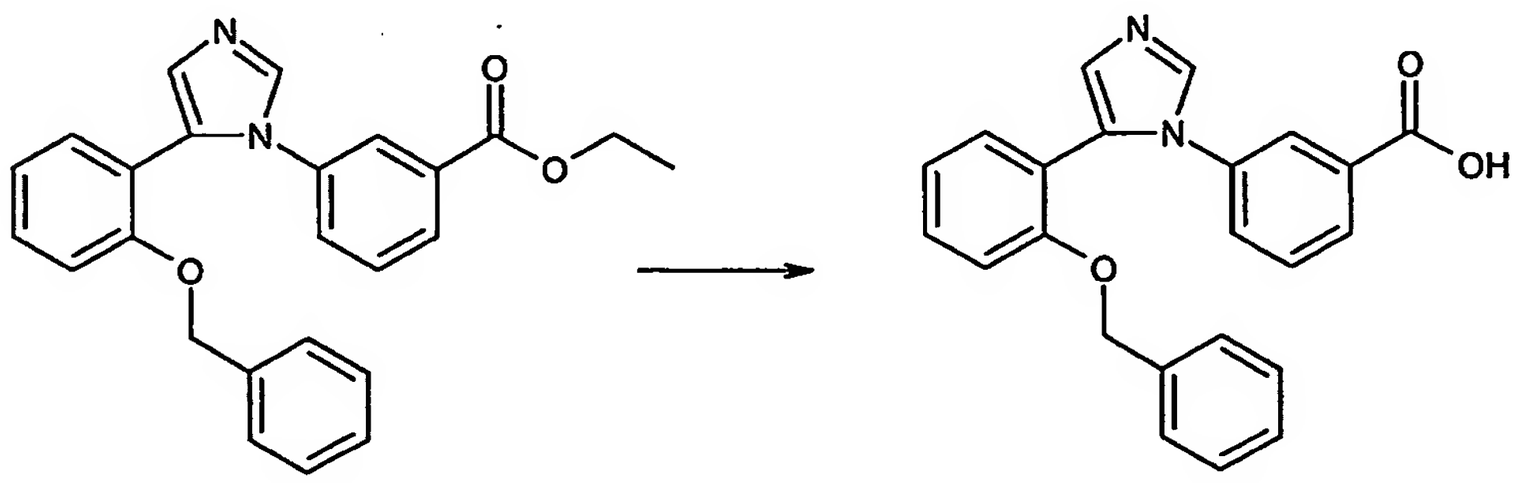
EXAMPLES

Example 1: 3-[5-(2-Benzyloxy-phenyl)-imidazol-1-yl]-benzoic acid

a) 3-[5-(2-Benzyloxy-phenyl)-imidazol-1-yl]-benzoic acid ethyl ester

2-Benzyloxy-benzaldehyde (0.38ml, 2.4mmol), ethyl-3-amino benzoate (0.36ml, 2.4mmol) and sodium sulfate (1.739g, 12.2mmol) were heated at reflux in toluene (4.8ml, 0.5M) for 20 hours. Upon cooling and the mixture was filtered and evaporated. The residue was dissolved in ethanol (10ml, 0.2M) and heated at reflux with potassium carbonate (1.422g, 10.3mmol) and tosylmethyl isocyanide (hereinafter referred to as "TosMIC") (604mg, 3.1mmol, 1.25eq) for 5 hours. The mixture was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated and the aqueous phase was extracted further with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, using Biotage, with iso-hexane containing ethyl acetate (30-50%) as eluant to yield the title compound (250mg, 27%).
^{1}H NMR ($CDCl_3$) 1.33 (3H, t, J=7Hz), 4.30 (2H, q, J=7Hz), 4.67 (2H, s), 6.80 (1H, d, J=8Hz), 6.93-7.03 (3H, m), 7.08-7.14 (1H, m), 7.20-7.31 (6H, m's excess), 7.33 (1H, dd, J=2Hz, J=7Hz), 7.73 (1H, s), 7.77 (1H, d, J=1Hz), 7.93 (1H, d, J=8Hz).

b) 3-[5-(2-Benzyloxy-phenyl)-imidazol-1-yl]-benzoic acid



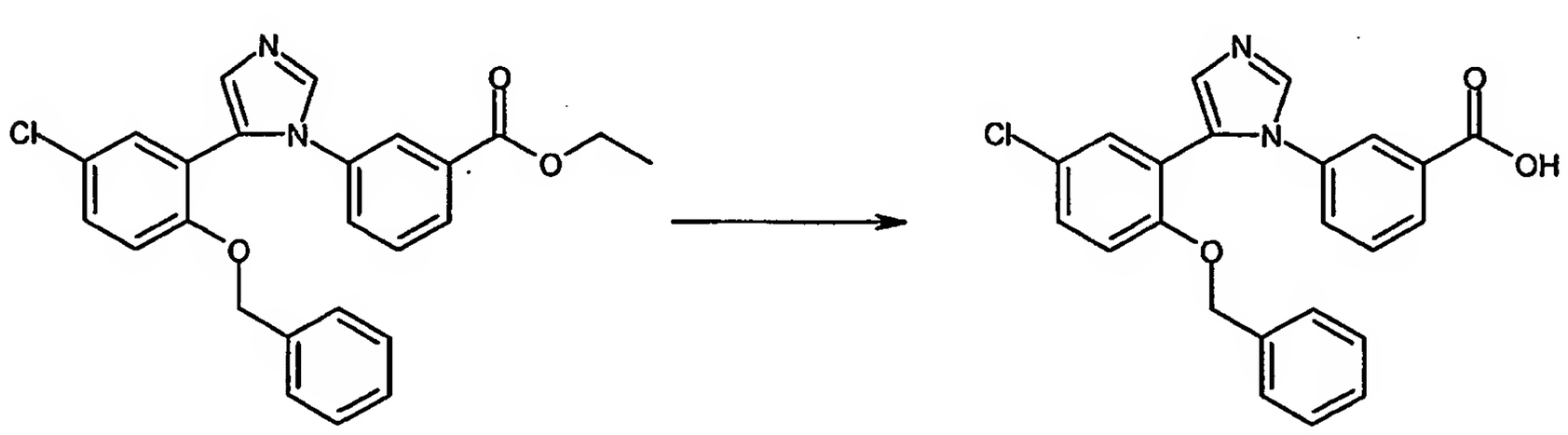
3-[5-(2-Benzyloxy-phenyl)-imidazol-1-yl]-benzoic acid ethyl ester (72mg, 0.2mmol) was heated at 90°C in mixture of ethanol (2ml) and 2M sodium hydroxide (1ml) in a reacti-vial for 4 hours. Upon cooling and dilution with ethyl acetate, the mixture was washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (59mg, 89%).
^{1}H NMR (MeOD) 4.82 (2H, s), 7.05 (1H, d, J=8Hz), 7.07-7.14 (3H, m), 7.28-7.55 (7H, m), 7.78 (1H, s), 7.91 (1H, s), 8.14 (1H, d, J=8Hz), 9.33 (1H, s).
LC/MS t=2.73 min [MH+] 371 [MH-] 369.

Example 2: 3-[5-(2-Benzyloxy-5-chloro-phenyl)-imidazol-1-yl]-benzoic acid

a) 3-[5-(2-Benzyloxy-5-chloro-phenyl)-imidazol-1-yl]-benzoic acid ethyl ester

2-Benzyloxy-5-chloro-benzaldehyde (513mg, 2.1mmol), ethyl-3-amino benzoate (0.31ml, 2.1mmol) and sodium sulfate (1.496g, 10.5mmol) were heated at reflux in toluene (4.2ml, 0.5M) for 20 hours. Upon cooling and the mixture was filtered and evaporated. The residue was dissolved in ethanol (10ml, 0.2M) and heated at reflux with potassium carbonate (1.487g, 10.8mmol) and TosMIC (528mg, 2.7mmol, 1.25eq) for 5 hours. The mixture was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated and the aqueous phase was extracted further with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, using Biotage, with iso-hexane containing ethyl acetate (30-50%) as eluant to yield the title compound (297mg, 33%).
^{1}H NMR ($CDCl_3$) 1.34 (3H, t, J=7Hz), 4.31 (2H, q, J=7Hz), 4.63 (2H, s), 6.71 (1H, d, J=9Hz), 6.90-6.97 (2H, m), 7.09-7.14 (1H, m), 7.20-7.28 (6H, m's excess), 7.31 (1H, d, J=8Hz), 7.34 (1H, d, J=3Hz), 7.72 (1H, s), 7.76 (1H, d, J=1Hz), 7.96 (1H, d, J=8Hz).

b) 3-[5-(2-Benzyloxy-5-chloro-phenyl)-imidazol-1-yl]-benzoic acid



3-[5-(2-Benzyloxy-5-chloro-phenyl)-imidazol-1-yl]-benzoic acid ethyl ester (94mg, 0.2mmol) was heated at 90°C in mixture of ethanol (2ml) and 2M sodium hydroxide (1ml) in a reacti-vial for 4 hours. Upon cooling and dilution with ethyl acetate, the mixture was washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (81mg, 93%).
^{1}H NMR (MeOD) 4.80 (2H, s), 7.03 (1H, d, J=9Hz), 7.05-7.11 (2H, m), 7.29-7.35 (3H, m), 7.38-7.56 (4H, m), 7.75 (1H, s), 7.90 (1H, s), 8.14 (1H, d, J=8Hz), 9.18 (1H, s).

LC/MS t=3.10 min [MH+] 405 & 407 [MH-] 403 & 405.

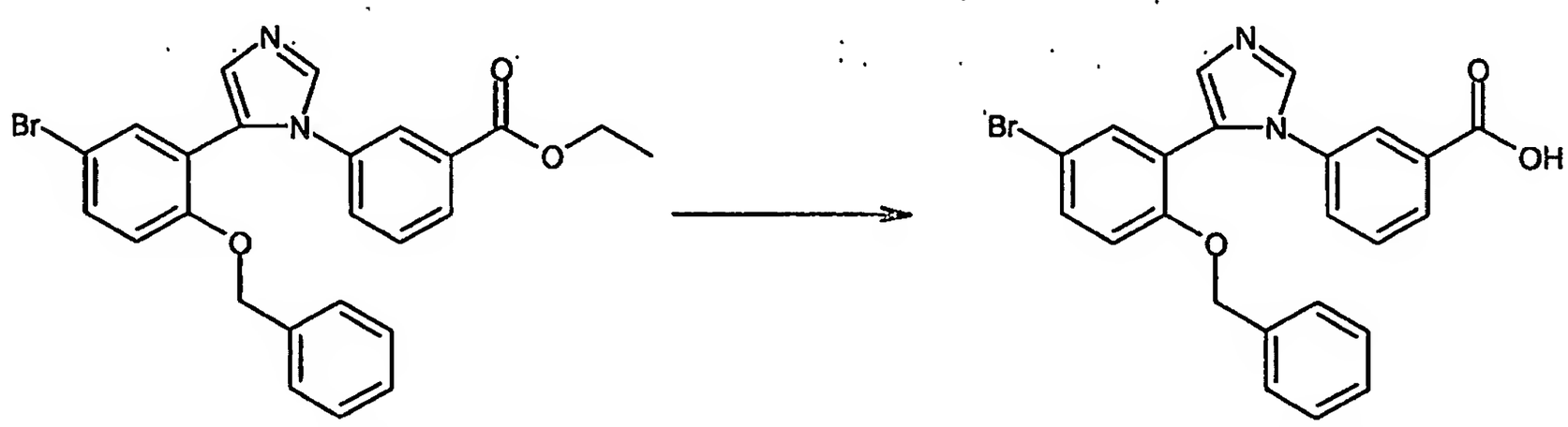
Example 3: 3-[5-(2-Benzyloxy-5-bromo-phenyl)-imidazol-1-yl]-benzoic acid

a) 3-[5-(2-Benzyloxy-5-bromo-phenyl)-imidazol-1-yl]-benzoic acid ethyl ester

2-Benzyloxy-5-bromo-benzaldehyde (516mg, 2.1mmol), ethyl-3-amino benzoate (0.31ml, 2.1mmol) and sodium sulfate (1.514g, 10.7mmol) were heated at reflux in toluene (4.2ml, 0.5M) for 6 hours. Upon cooling and the mixture was filtered and evaporated. The residue was dissolved in ethanol (10ml, 0.2M) and heated at reflux with potassium carbonate (1.570g, 11.4mmol) and TosMIC (577mg, 3.0mmol, 1.25eq) for 2.5 hours. The mixture was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated and the aqueous phase was extracted further with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, using Biotage, with iso-hexane containing ethyl acetate (30-50%) as eluant to yield the title compound (480mg, 57%).

^{1}H NMR ($CDCl_3$) 1.35 (3H, t, J=7Hz), 4.32 (2H, q, J=7Hz), 4.62 (2H, s), 6.66 (1H, d, J=9Hz), 6.89-6.96 (2H, m), 7.09-7.15 (1H, m), 7.21-7.28 (4H, m's excess), 7.31 (1H, t, J=7Hz), 7.38 (1H, dd, J=2Hz, J=8Hz), 7.49 (1H, d, J=2Hz), 7.71 (1H, s), 7.76 (1H, d, J=1Hz), 7.96 (1H, d, J=8Hz).

b) 3-[5-(2-Benzyloxy-5-bromo-phenyl)-imidazol-1-yl]-benzoic acid



3-[5-(2-Benzyloxy-5-bromo-phenyl)-imidazol-1-yl]-benzoic acid ethyl ester (112mg, 0.2mmol) was heated at 90^{o}C in mixture of ethanol (2ml) and 2M sodium hydroxide (1ml) in a reacti-vial for 3 hours. Upon cooling and dilution with ethyl acetate, the mixture was washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (92mg, 87%).

^{1}H NMR ($CDCl_3$) 4.81 (2H, s), 6.99 (1H, d, J=9Hz), 7.05-7.12 (2H, m), 7.30-7.35 (3H, m), 7.39-7.44 (1H, m), 7.53 (1H, t, J=8Hz), 7.60 (1H, dd, J=2Hz, J=9Hz), 7.65 (1H, d, J=2Hz), 7.79 (1H, s), 7.91 (1H, s), 8.15 (1H, d, J=8Hz), 9.26 (1H, s).

LC/MS t=3.15 min [MH+] 449 & 451 [MH-] 447 & 449.

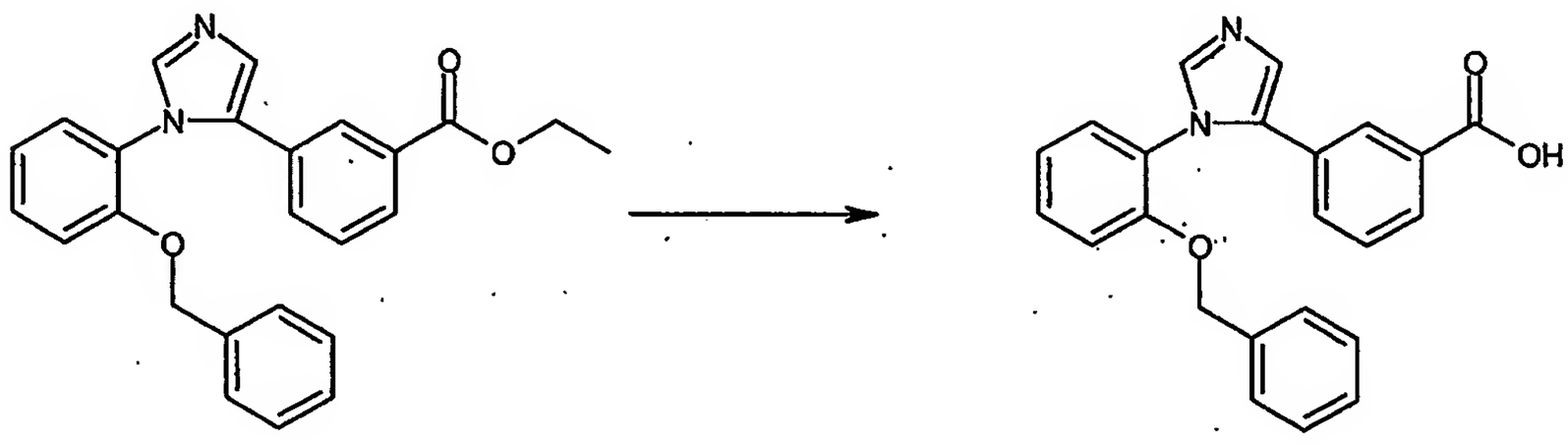
Example 4: 3-[5-(2Benzyloxy-phenyl)-3*H*-imidazol-4-yl]-benzoic acid

a) 3-[5-(2-Benzyloxy-phenyl)-3H-imidazol-4-yl]-benzoic acid ethyl ester

2-Benzyloxy-aniline (628mg, 3.1mmol), 3-formyl-benzoic acid methyl ester (505mg, 3.1mmol) and sodium sulfate (2.200g, 15.5mmol) were heated at reflux in toluene (6.2ml, 0.5M) for 20 hours. Upon cooling and the mixture was filtered and evaporated. The residue was dissolved in ethanol (15ml, 0.2M) and heated at reflux with potassium carbonate (2.130g, 15.0mmol) and TosMIC (798mg, 4.1mmol, 1.25eq) for 20 hours. The mixture was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated and the aqueous phase was extracted further with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography, using Biotage, with iso-hexane containing ethyl acetate (30-50%) as eluant to yield the title compound (216mg, 18%).

^{1}H NMR ($CDCl_3$) 1.31 (3H, t, J=7Hz), 4.28 (2H, q, J=7Hz), 4.88 (2H, s), 6.95-7.05 (4H, m), 7.20-7.30 (6H, m's excess), 7.33-7.40 (2H, m), 7.65 (1H, d, J=1Hz), 7.82 (1H, d, J=1Hz), 7.85-7.90 (1H, m).

b) 3-[5-(2Benzyloxy-phenyl)-3*H*-imidazol-4-yl]-benzoic acid



3-[5-(2-Benzyloxy-phenyl)-3*H*-imidazol-4-yl]-benzoic acid ethyl ester (68mg, 0.2mmol) was heated at 90°C in mixture of ethanol (2ml) and 2M sodium hydroxide (1ml) in a reacti-vial for 4 hours. Upon cooling and dilution with ethyl acetate, the mixture was washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (37mg, 59%).

^{1}H NMR (MeOD) 4.99 (2H, s), 7.06-7.13 (2H, m), 7.19 (1H, t, J=8Hz), 7.24-7.34 (4H, m), 7.37-7.48 (2H, m), 7.55-7.63 (2H, m), 7.88-7.94 (2H, m), 8.06 (1H, d, J-7Hz), 9.14 (1H, s). LC/MS t=2.69 min [MH+] 371 [MH-] 369.

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

The ability of compounds to antagonise EP_1 & EP_3 receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of EP_1 or EP_3 receptors by the natural agonist hormone prostaglandin E_2 (PGE_2). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE_2 can mobilise. The net effect is to displace the PGE_2 concentration-effect curve to higher concentrations of PGE_2. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP_1 or EP_3 calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP_1 or EP_3 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10µg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE_2 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE_2 (pIC_{50}) may then be estimated.

<u>Binding Assay for the Human Prostanoid EP_1 Receptor</u>

Competition assay using $[^3H]$-PGE2.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E_2 ($[^3H]$-PGE_2) for binding to the human EP_1 receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP_1 cDNA has previously been transfected. Cells are cultured in suitable

flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10μg/ml puromycin and 10μM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid (Na_2EDTA) and 10μM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na_2EDTA, 140mM NaCl, 10μM indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed three times by suspension and centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na_2EDTA, 10mM $MgCl_2$ (pH 6). Aliquots are frozen at –80°C until required.

For the binding assay the cell membranes, competing compounds and [^{3}H]-PGE_2 (3nM final assay concentration) are incubated in a final volume of 100μl for 30 min at 30°C. All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding (IC_{50}).

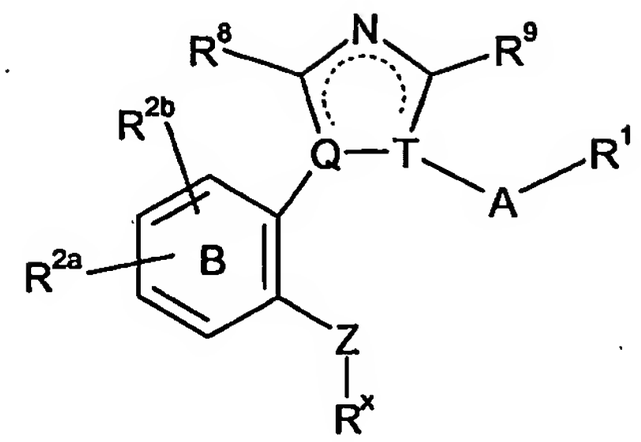
By application of this technique, compounds of the examples had an antagonist pIC_{50} value of between 7.0 and 9.5 at EP_1 receptors and pIC50 value of < 6.0 at EP_3 receptors.

No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO_2;

R^1 represents CO_2R^4, CN, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted SO_2heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR^7;

R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

either Q is carbon and T is nitrogen, or

Q is nitrogen and T is carbon; and

the dotted line represents alternating single and double bonds;

R^8 and R^9 independently represent hydrogen, halogen, C_{1-3}alkyl or CF_3;

Q^a and Q^b are independently selected from hydrogen and CH_3;

wherein when A is a 6-membered ring the R^1 substituent and imidazole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and imidazole ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
or a derivative thereof.

2. A compound according to claim 1 wherein A is optionally substituted phenyl.

3. A compound according to claim 1 or claim 2 wherein R^x is optionally substituted CH_2phenyl.

4. A compound according to any one of claims 1 to 3 wherein R^{2b} is hydrogen or halogen.

5. A compound according to any one of claims 1 to 4 wherein R^{2b} is positioned 1,4- relative to the Z substituent and 1,3- relative to the phenyl ring.

6. A compound selected from:
3-[5-(2-Benzyloxy-phenyl)-imidazol-1-yl]-benzoic acid;
3-[5-(2-Benzyloxy-5-chloro-phenyl)-imidazol-1-yl]-benzoic acid;
3-[5-(2-Benzyloxy-5-bromo-phenyl)-imidazol-1-yl]-benzoic acid; and
3-[5-(2-Benzyloxy-phenyl)-3*H*-imidazol-4-yl]-benzoic acid;
and derivatives thereof.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof together with a pharmaceutical carrier and/or excipient.

8. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for use as an active therapeutic substance.

9. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

10. A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

11. A method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method

comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

12. A method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof.

13. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

14. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

15. Use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

16. A compound of formula (I) or a derivative thereof, according to claim 1, substantially as hereinbefore described with reference to any one of the Examples.

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(74) Agent: **RUTTER, Keith**; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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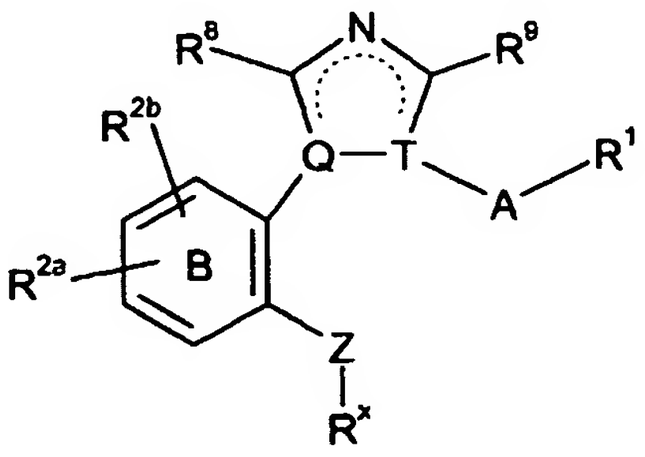
(54) Title: PHENYL SUBSTITUTED IMIDAZOLE DERIVATIVES



(I)

(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable derivative thereof: wherein A, B, Z, R^1, R^{2a}, R^{2b}, R^x, R^8, R^9, Q, and T are as defined in the specification, a process for the preparation of such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002831

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/54 A61K31/4164 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/19814 A (MERCK FROSST CANADA INC ; RUEL REJEAN (CA); LABELLE MARC (CA); LACOMBE) 22 March 2001 (2001-03-22) examples	1-16
Y	WO 02/15902 A (MERCK FROSST CANADA INC ; NANTEL FRANCOIS J (CA); TURNER MERVYN (CA);) 28 February 2002 (2002-02-28) examples	1-16
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P,Y	WO 03/101959 A (GIBLIN GERARD MARTIN PAUL ; MILLER NEIL DEREK (GB); HALL ADRIAN (GB);) 11 December 2003 (2003-12-11) examples	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2004	07/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Menegaki, F

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/002831

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-12
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/002831

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